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PATENT COOPERATION TREATY

Rec'd PCT/TO 20 JUL 2004

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
HeL/AO 49908		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000092	21.01.2003	21.01.2002
International Patent Classification (IPC) or national classification and IPC		
A61K 9/20		
Applicant		
Galenica AB Medeon et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:

   ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

   ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

   _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.08.2003	27.04.2004
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Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000092

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-18 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 19 received by this Authority on 23.02.2004
pages* _____ received by this Authority on _____

☒ the drawings:

pages 1/1 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-5, partly

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5
are so unclear that no meaningful opinion could be formed *(specify)*:

Present claims 1-5 relate to a composition-forming process which is defined in part by the properties of the substances that are incorporated into the composition, the substances used described in general terms, as well as the properties of the composition thus produced. The expressions that describe those properties (non-swellable, oil, surfactant, polar liquid, self-emulsifying, self-dispersing and immediate

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III.1

release) are not always explicitly used in the literature. Furthermore, support within the meaning of Article 6 PCT is to be found for only a small proportion of the compounds that fall under the properties mentioned above. Thus, a complete search of the whole scope of the claims cannot be performed.

The search has been carried out for a process which involves those compounds that are listed in the description.

Further, the search has covered the general aspects of the invention to some extent, although it lacks the necessary precision in the definition of the subject matter. Consequently, the search for the general concept of a process for the preparation of a self-dispersing or self-emulsifying immediate release tablet will retrieve a pertinent document only if this concept is described in general terms in a reference. Specific processes or tablets previously known and falling under the general concept - but failing to mention this fact - are likely not to be revealed in such a search.

Consequently, the opinion is formed on basis of the search performed.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000092

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-5	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Documents from the international search report:

A. Schwarz J. et al., Increased bioavailability of coenzyme Q-10 in self-emulsifying controlled release tablet: New type of delivery system for hydrophobic drugs. Proc. Int. Symp Cont. Rel. Bioact. Mater. 28 (2001) 824-825
B. Schwarz J. et al., Self-emulsifying controlled release tablet: New type of delivery system for hydrophobic drugs. Proc. Int. Symp Cont. Rel. Bioact. Mater. 27 (2000) 395-396
C. WO0041676 A1
D. WO9423700 A1
E. FR2710535 A1
F. Sugao H. et al., Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated microparticles. J Pharm Sci., 87 (1998) 96-100

Documents A and B both refer to a self-emulsifying delivery system, where an active material is dissolved or dispersed in a lipid/surfactant phase to form a stable microemulsion. The microemulsion is granulated with gel forming water-soluble polymers and other excipients, dried, milled and compressed into traditional tablets.

The main difference between the present application and documents A-B is the resulting type of delivery; according to the present application, a self emulsifying immediate release tablet is construed when a granulation medium containing lipophilic active substance, oil, surfactant and polar liquid is mixed with non-swellable filler and optionally binder, dried, milled and compressed into tablets. Documents A-B use the same method of manufacture, with a resulting controlled-release tablet.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Document C discloses a self-emulsifying system for hydrophobic and water-sensitive agents. The system provides a solid dosage form, e.g. tablets. Microcrystalline cellulose is mixed with an oily substance, surfactant and water, granulated, extruded, spheronized and dried. The pellets so formed are suitable for tabletting or for filling into capsules. Thus, from document C, a process for the preparation of self-dispersing or self-emulsifying tablets is known.

The invention according to claims 1-5 moreover differs from documents A-C in that the surfactant is specified to be selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol. However, since these surfactants are well known to the person skilled in the art, this selection cannot in itself be considered to involve an inventive step.

Document D pertains to a solid preparation for substantially immediate release of an active agent with low or very low solubility. The composition according to document D does not include oil in the granulation medium. However, in other aspects, the process for production of the preparation corresponds to the method used according to the present application; i.e. solubilizing agents and water constitute the granulation medium, microcrystalline cellulose is a filler and pellet forming material. The granulation medium may be heated prior to addition to the filler. The active agent may form part of the granulation medium, or may be mixed with the filler prior to the addition of the granulation medium. Solubilizing agents include PEG 400 and PEG 40 hydrogenated castor oil.

In document E, a composition that is solid at room temperature, and liquid at body temperature, is produced from an active agent, a lipophilic phase, a surfactant and a co-surfactant. A microemulsion is formed when the composition is ingested. There is, however, no information as to how the composition is manufactured.

Document F concerns coating of a microparticle. The coating comprises hydrogenated oil and surfactants. The document is considered to disclose prior art and will not be further adressed.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Thus, all documents A-C pertain to processes for the preparation of self-dispersing or self-emulsifying tablets. These documents are considered to represent the closest prior art.

Documents A and B explicitly discloses a granulation medium in the form of a microemulsion. In document C, the type of lipophilic-hydrophilic dispersion is not identified. Thus, the difference between claims 3 and 4 of the present application, and the processes according to documents A-C is that claims 3-4 suggest that the granulation medium be an emulsion or a liquid crystal phase. However, the presence of all claims 2-4 implies that the type of lipophilic-hydrophilic dispersion is not central to the application, and therefore, these claims lack the requirement of inventive step.

In conclusion, claims 1-5 are new but lack the requirement of inventive step.

CLAIMS

1. A process for the preparation of a self-dispersing or self-emulsifying immediate release tablet comprising the following steps,

mixing a granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

granulation of said mixture into granules,

drying of said granules,

sieving of the granules into a size below 1 mm,

mixing of the granules with tabletting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil, a surfactant and a polar liquid.

2. A process according to claim 1, characterised in that the granulation medium is a microemulsion.

3. A process according to claim 1, characterised in that the granulation medium is an emulsion.

4. A process according to claim 1, characterised in that the granulation medium is a liquid crystalline phase.

5. A process for the preparation of a self-dispersing immediate release tablet comprising the following steps,

mixing a heated granulation medium containing an active lipophilic substance with one or more non-swellable fillers and optional binders,

granulation of said mixture into granules which are allowed to cool,

sieving of the granules into a size below 1 mm,

mixing of the granules with tabletting aids, and

compressing said mixture into tablets, characterised in that the granulation medium comprises an oil and a surfactant.

6. A process according to any of claims 1-5, characterised in that the surfactant is selected from the group consisting of fatty acid esters of glycerol, and fatty acid esters of polyethylene glycol.

7. A tablet, characterised in being prepared by a process according to any of claims 1-6.